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EXAMINER

SWITZER, JULIET CAROLINE

ART UNIT PAPER NUMBER

1634

DATE MAILED: 11/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/864,954

Applicant(s)

KAUL ET AL.

Examiner

Juliet C. Switzer

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 August 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 2 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-2 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 8/21/03. Claims 1-2 have been amended. Claims 1-2 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Claim Objections

2. Claim 1 is objected to because of the following informalities: in the newly added portion of the claim the word "amound" appears to be a misspelling of the word "amount." Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The previous rejections under 112 2nd have been withdrawn in view of applicant's amendments to the claims.
4. Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to processes for determining whether or not a test sample originating from or containing human cells has a tumor progression potential which comprises steps of incubating samples under stringent hybridization conditions with a nucleic acid probe which is selected from: a nucleic acid with a sequence of SEQ ID NO: 1, the complement or a nucleic acid that hybridizes under stringent conditions with of a nucleic acid with a sequence of

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SEQ ID NO: 1, quantifying the approximate amount of hybridization, and comparing the hybridization levels between two samples or between the probe and a housekeeping gene. The scope of the claims thus includes the detection of tumor progression potential for any type of cancer, hybridization using any nucleic acid which comprises instant SEQ ID NO: 1 or any smaller portion of SEQ ID NO: 1 that hybridizes to SEQ ID NO: 1 under any stringency conditions. The claims are limited to using human samples.

The specification teaches an isolated nucleic acid referred to as PKW, and asserts that this nucleic acid is upregulated in tumor cells (§ 0102). Instant SEQ ID NO: 1 is the cDNA of the PKW gene encoding a large PKW splice variant and encodes instant SEQ ID NO: 2 (§ 0118 and § 154). Turning to the figures and the examples, Figure 1 shows that PKW is expressed in only one of the primary carcinoma cell lines tested, namely cell line AR derived from medullary mammary carcinoma (§ 0112). PKW was not expressed in cell lines derived from invasive ductal mammary carcinoma, or from additional cell lines derived from carcinoma bone marrow micrometastases and malignant ascites fluid. Figure 2 shows that PKW was detected in cell line AR (cell E6 and H6) but not in any of a number of other tissues or cell lines (§ 0114). Figure 4 shows the detection of transcripts of gene PKW in mammary carcinomas by RT-PCR as described in Example 9. Figure 4 shows PKW was detected in cell line AR and also in two additional “different mammary carcinoma samples (§ 115).” The specification at § 0153 states that a panel of mammary carcinoma cell lines described in Schwirzke *et al.* tested negative for expression of the PKW by northern blotting and by RT-PCR. The cell lines in this panel include metastatic breast cancer cell lines, a ductal carcinoma cell line (T47D), as well as breast adenocarcinoma cell lines. The specification at § 153 states that “In summary 11 mammary

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carcinomas were analyzed for expression of the small transcript gene of PKW by RT-PCR. 4 carcinomas scored positive... Two of the positive carcinomas corresponded to ductal carcinomas and the other two matched with lobular carcinomas.” However, the specification does not clearly show the data that support this statement. The specification discusses the isolation of RNA from Breast Tumor tissues (Example 8, ¶ 0165), but never provides any indication that this RNA was assayed for the presence of instant SEQ ID NO: 1. Thus, the specification demonstrates that the PKW gene is expressed in some breast carcinoma cell lines but not others. Specifically, the specification demonstrates expression of PKW in a cell line derived from medullary mammary carcinoma (the AR cell line) and asserts that PKW is expressed in two ductal carcinomas and two lobular carcinomas. The specification also demonstrates that PKW is not expressed in cell lines derived from invasive ductal mammary carcinoma (cell line AR and T47D), or from additional cell lines derived from carcinoma bone marrow micrometastases, ductal carcinomas, breast adenocarcinomas and malignant ascites fluid.

The over-expression of PKW in some breast cancer cell lines is not sufficient evidence to enable one skilled in the art to determine that this protein would necessarily be over-expressed in primary tumor tissue as compared to non-tumor tissue. The prior art teaches that with regard to the correlation between cancer cell lines and primary tumor tissue relationships and are highly unpredictable. Dermer *et al.* (Biotechnology Vol. 12, March 1994, p. 320) teach that cell lines are a poor representation of malignancy because they have survived crisis and have adapted an immortal life in culture, and thus has been enabled to survive in its artificial environment. Dermer *et al.* state that “the petri dish cancer is really a poor representation of malignancy, with characteristics profoundly different from the human disease.” Further, Chabert *et al.* (Int. J.

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Cancer: 53, 837-842 (1993)) compare PARP gene expression, enzymatic activity and quantities in 3 animal tumor cell lines in culture verses those transplanted into a compatible host, and found that, for “a given tumor cell line, marked differences exist in poly(ADPR)P gene expression and enzymatic activity between cultured cells and cells obtained from solid or ascitic tumors.

Indeed, poly(ADPR)P gene expression, endogenous activity and amount are higher in exponentially growing cells than in *in vivo* tumors (p. 837, see also Fig. 1).” Chabert *et al.* further suggest that such discrepancies in enzymatic activity between cell culture and *in vivo* growth conditions exist because of differences in proliferation rates and/or environmental conditions (p. 841). Odum *et al.* (Toxicology in Vitro 12 (1998) 273-278) also teach that breast cancer cell lines respond to xenobiotic estrogens in an unpredictable manner. Though Odum *et al.* are not screening for gene expression in particular, their disclosure underscores the unpredictable behavior breast cancer cell lines versus primary tumor tissue.

Furthermore, even if the use of cell lines were sufficient to establish a relationship between some primary cancers and gene expression, the conflicting data presented in the instant specification demonstrates the unpredictability of interpreting the results of the instantly claimed screening methods since the data in the specification is unclear as to precisely which breast cancers can be predicted based on the instant screening methods. For example, the teachings of the specification indicate that the instant PKW gene was expressed in some ductal cancer cell lines but not other ductal cancer cell lines. The teachings of the specification do not provide reliable guidance as to which cancers can be predicted using the claimed methods.

As a further point, the instant claims encompass using a variety of variants of SEQ ID NO: 1, including fragments of SEQ ID NO: 1 and sequences that differ from SEQ ID NO: 1 but

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that would hybridize to SEQ ID NO: 1 as a probe within the detection methods claimed herein. However, the specification does not provide any guidance or description as to which shorter pieces or variants of instant SEQ ID NO: 1 can be used as probes while retaining the ability to detect the PKW gene itself and as an indication of the presence of tumor progression potential. Fragments of SEQ ID NO: 1 are contained within a variety of human proteins, for example, Wang *et al.* (US 2002/01686371) teaches a gene that is differentially expressed in lung cancer (their SEQ ID NO: 1065) that shares 19 nucleotides in common with instant SEQ ID NO: 1 (nucleotides 49-67 of their SEQ ID NO: 1065 are identical to the complement of nucleotides 1906-1924 of instant SEQ ID NO: 1). Thus, this is a nucleic acid that has a fragment of SEQ ID NO: 1, the use of which is encompassed within the instant claims but which is associated with lung cancer. The specification has not provided any guidance as to which fragments of instant SEQ ID NO: 1 are useful as hybridization probes for determining whether or nor a test sample has tumor progression potential, or how portions of SEQ ID NO: 1 could be modified (i.e. to obtain sequences that hybridize to SEQ ID NO: 1 but are not contiguous sequences of SEQ ID NO: 1) and still retain their ability to be used as hybridization probes for determining whether or nor a test sample has tumor progression potential.

While the ordinary practitioner in this field is highly skilled, the evidence presented in the specification does not provide even a highly skilled practitioner means to overcome the limitations of evidence derived from cell lines and to make and/or use instant SEQ ID NO: 1 or fragments thereof as a method for cancer diagnosis and/or detection with any reliability. As discussed by Dermer *et al.*, Chabert *et al.* and Odum *et al.*, the level of predictability between the activity of tumor cell lines and actual tumor tissue is very low, and thus practicing this invention

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would require unreasonable experimentation on the part of the practitioner to further screen actual tumor tissue to test for a connection between instant SEQ ID NO: 1 over-expression and cancer. Further, the specification does not enable the skilled artisan to detect all types of cancer, as the language of the claims permits. The specification is unclear even which types of breast cancer can be detected. Beyond that, the specification does not provide any guidance as to which portions of instant SEQ ID NO: 1 would be sufficient for the detection of breast or any other cancer. In light of the teachings in the prior art, and the general unpredictability concerning the activity of instant SEQ ID NO: 1 in tumor cell lines versus actual tumor tissue, the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Response to Remarks

With regard to the enablement rejection, applicants submit that the present invention is not trying to predict any specific type of cancer, but rather, is trying to show that expression of PKW in any cell **may** be indicative of a cell having tumor progression potential. Applicant's own language in this argument underscore the examiner's point. PKW might be indicative of tumor progression potential, but it might not. Applicant's specification has not provided sufficient data to determine which is the case, and for this reason, in view of a consideration of each of the factors in the rejection, it is concluded that it would require undue experimentation to practice the claimed invention. Indeed, one would have to establish that the PKW nucleic acid (instant SEQ ID NO: 1) is associated with tumor progression potential in any and all cancers, as is suggested by the claims. Applicant's specification has not provided any evidence to

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demonstrate that cells that express or overexpress PKW have “tumor progression potential” any more than a cell that does not express or overexpress PKW. The reasoning for this conclusion is clearly elucidated in the grounds of rejection. Applicant’s own data are only based on expression of this gene in some (a limited few) breast cancer **cell lines**, which themselves are not reliable markers of tumor activity, as discussed in the rejection. Yet applicant’s claim purports to be a predictive assay that a particular cell has potential to develop into some kind, any kind of tumor. For the reasons discussed in the rejection, it is maintained that the specification is not enabling for the claimed invention.

Applicant cites paragraph [133] of the specification as teaching that “in accordance with the present invention, the PKW nucleic acid is expressed in a greater amount in a tumor sample than in a sample free from tumor cells...” However, the specification provides only data and evidence relating to tumor cell **LINES**, not tumor cells from primary tumors. These are not reliable predictors of activity in actual tumors, as discussed in the specification. Thus, the rejection is maintained.

Conclusion

5. No claims are allowed.
6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

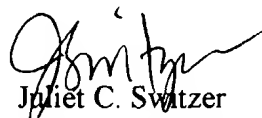
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is 703 306 5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on 703 308 1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703 305 3592 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 0196.



JEFFREY FREDMAN
PRIMARY EXAMINER



Juliet C. Switzer
Patent Examiner
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November 4, 2003